Original research

Association of diastolic and renal dysfunctions in non-ST segment elevation acute coronary syndrome patients with heart failure with preserved ejection fraction and their impact on outcomes

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Abstract

Objective: The presence and progression of renal dysfunction can increase the incidence of cardiovascular complications and increase the risk of mortality in patients with heart failure and acute coronary syndrome. The aim of the study was to explore association of renal and left ventricular diastolic (LVDD) dysfunctions in patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS) with heart failure with preserved LV ejection fraction (HFpEF) and their impact on outcomes.

Methods: The study included 58 patients with NSTE-ACS and HFpEF, who were divided depending on the type of LVDD into 2 groups: the 1st group included patients with LVDD grade I (n=33), the 2nd group included patients with LV DD grade II (n=25). Glomerular filtration rate, daily microalbuminuria and daily protein excretion were calculated, and echocardiographic examination was performed at the time of admission to the hospital and 3 months after discharge from the hospital. In addition, coronary angiography was performed during the hospitalization period.

Results: Renal dysfunction was found in 49 (84.48%) patients with NSTE-ACS with HFpEF. In the group 1, renal dysfunction was detected in 26 (78.8%) (95% CI 71.2%; 88.8%) cases, while in the 2nd group renal dysfunction occurred even more often – in 23 (92.0%) (95% CI 80.7%; 105.8%) patients (p<0.0001). Indicators of renal function significantly correlated with all indicators of LV diastolic function. Predictors of reduced renal function are echocardiographic parameters of LVDD, the size of the left atrium, N-terminal pro b-type natriuretic peptide (NT-proBNP) and an increase in the end-systolic area of the right ventricle. During a prospective observation of patients with NSTE-ACS with HFpEF in the third month, chronic kidney disease (CKD) developed in 26 (44.83%) patients. In the 1st group of patients CKD was detected in 3 (9.1%) (95% CI 3.1%; 23.1%), and in the 2nd group - in 23 (92%) (95% CI 80.7%; 105.8%) of patients (p<0.0001). A prospective three-month follow-up revealed the development of CKD, the rate of re-hospitalization was 11.4% (95% CI 0.8%; 22.0%, p=0.021), while HF symptoms worsened in 14.3% (95% CI 3.3%; 26.5%, p=0.008). CKD had an adverse impact on outcomes in patients with NSTE-ACS and HFpEF, as evidenced by an increased risk of re-hospitalization (odds ratio [OR] 2.474, 95% CI 1.748-3.500, p<0.0001), recurrence of ACS (OR 2.120, 95% CI 1.594-2.819, p<0.024), and progression of HF (OR 2.647, 95% CI 1.819-3.851, p<0.0001). Our study found that prognostically significant indicators of readmission and recurrent ACS are estimated glomerular filtration rate and NT-proBNP levels, and possible progression of HF is predicted by the level of daily microalbuminuria. The results of coronary angiography showed a tendency to differences in the groups of patients with NSTE-ACS with HFpEF.

Conclusion: Renal function indicators in patients with NSTE ACS with HFpEF are significantly associated with diastolic parameters of the left ventricle and depend on the severity of diastolic dysfunction of the left ventricle. Predictors of readmission, recurrence of acute coronary syndrome, and progression of chronic heart failure are glomerular filtration rate, daily microalbuminuria, daily proteinuria, and left ventricular end-diastolic volume.

Key words: left ventricle, diastolic dysfunction, heart failure, renal function, acute coronary syndrome, prognosis
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Graphical abstract

Association of diastolic and renal dysfunctions in non-ST segment elevation acute coronary syndrome patients with heart failure with preserved ejection fraction and their impact on outcomes			
Variables	**Grade I LV DD**	**Grade II LV DD**	**Overall**
Renal dysfunction prevalence on admission	78.8% (95% CI: 71.2% - 88.8%)	92.0% (95% CI: 80.7% - 105.8%)	84.48%
CKD after three months	9.1% (95% CI: 3.1% - 23.1%)	92.0% (95% CI: 80.7% - 105.8%)	44.83%
Rehospitalization	Not found	11.4% (95% CI: 0.8% - 22.0%)	11.4%
Progression of HF	Not found	14.3% (95% CI: 3.3% - 26.5%)	14.3%
Predictors of outcomes	eGFR, NT - proBNP levels	eGFR, NT -proBNP levels, microalbuminuria	-
Coronary angiography	Trends in differences		-
	In the case of CKD		
Odds ratio for rehospitalization	2.474 (95% CI: 1.748 - 3.500)		
Odds ratio for recurrence of ACS	2.120 (95% CI: 1.594 - 2.819)		
Odds ratio for progression of HF	2.647 (95% CI: 1.819 - 3.851)		

Introduction

As is known today myocardial ischemia leads to left ventricle diastolic dysfunction (LV DD) which in turn underlies the development of heart failure (HF). Moreover, the severity of LV DD (grade II or III) has prognostic significance for future hospitalization for HF (1). Cardiac diastolic dysfunction refers to increased stiffness and impaired relaxation of the LV, leading to impaired filling during diastole (2). Despite this simple definition, truly understanding the cause of diastole changes, as well as its relationship to myocardial ischemia and renal dysfunction, is extremely complex. Ischemic heart disease, LV DD and chronic kidney disease (CKD) are interrelated. Myocardial ischemia plays an important role in the pathophysiology of HF and CKD through the influence of LV diastolic function on cardiac and renal function. Because systematic coronary angiography is not always possible in clinical practice in all patients hospitalized for HF, many studies are limited by retrospective designs and varying definitions of coronary artery disease based only on the patient's medical history or myocardial ischemia detected by electrocardiogram or noninvasive stress tests.

Despite the fact that numerous studies have been devoted to changes in renal function in HF, there is no data on its connection with impaired renal function and the severity of LV DD. There are still no specific data on the diagnosis of cardiorenal syndrome in HF with preserved ejection fraction (HFpEF).

Detection of the onset or progression of cardiorenal syndrome is of paramount importance for optimal treatment and can contribute to increasing the life expectancy of both patients with preserved EF and those with limited EF. Consequently, timely diagnosis of renal dysfunction in HF and acute coronary syndrome makes it possible to begin early treatment, which will prevent the addition of severe cardiorenal complications with a decrease in mortality and an improvement in the prognosis of this complex group of patients.

The aim of the study was to explore association of renal and diastolic dysfunctions of the left ventricular in patients with NSTE-ACS with HFpEF and their impact on outcomes.

Methods

Study design and population

Our study is prospective observational.

We examined 58 patients with NSTE-ACS with symptoms of HFpEF and LV ejection fraction (LVEF) ≥50%, admitted to the Department of Urgent Cardiology of the National Center for Cardiology and Therapy named after Academician Mirsaid Mirrakhimov. Criteria for inclusion in the study were: clinical symptoms of NSTE-ACS, transient ST segment depression, presence of symptoms and/or signs of HF, echocardiography data (left atrial (LA) dilatation, LVDD), elevation of N-terminal pro B-type natriuretic peptide (NT-proBNP) levels. Exclusion criteria from the study were: having previously suffered an acute myocardial infarction, myocarditis, pathologies of the valvular structure of the heart, hypertension, atrial fibrillation, left and right bundle branch block, atrial arrhythmias, previous percutaneous coronary intervention/ coronary artery bypass grafting, implanted pacemaker, liver failure, diabetes, glomerulonephritis, renal artery stenosis, chronic pulmonary disease, and cancer. The patients were divided into two groups: 1st group with LV DD grade I (n=33) and 2nd group with grade II of LV DD (n=25).

Informed consent was taken before procedure from patients. This study complies with the Declaration of Helsinki and was performed according to the National Centre of Cardiology and Internal Medicine Ethics Committee approval.

Baseline variables

All 58 patients, in accordance with the assigned tasks, underwent a clinical, laboratory and instrumental examinations, including collection of complaints and anamnesis, physical examination, standard measurement of blood pressure, measurement of daily diuresis, general analysis of the main parameters of blood, urine, biochemical blood tests, with mandatory determination of NT-proBNP and creatinine levels with further analysis of glomerular filtration rate (GFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) formula, albumin and protein in 24-hour urine, electrocardiography (ECG) in 12 standard leads and transthoracic echocardiography.

Operational definitions

The diagnosis of NSTE-ACS was based on the ESC Guidelines for the for the management of acute coronary syndromes 2023 (3).

Confirmation of the diagnosis of HF was based on the following criteria (ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, 2021) (4):

- Clinical symptoms and signs of HF;
- Echocardiography data (left atrial dilatation, LV DD);
- Increased level of NT-proBNP more than 125 pg/ml.

The presence of LV DD was diagnosed according to the criteria of the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging from 2016 (2).

Renal dysfunction was defined as the presence of one of the following indicators (5):

- Estimated GFR <60 ml/min/1.73m^2;
- Daily albumin excretion >30 mg/day;
- Daily protein excretion >150 mg/day.

Determination of renal function

To assess renal function in all patients, GFR was calculated using the CKD-EPI formula (modified 2021). Albuminuria and proteinuria were quantified in urine collected over a 24-hour period. Daily protein excretion in urine was studied by the traditional method with sulfosalicylic acid using a photoelectric calorimeter. Albuminuria in 24-hour urine was analyzed using the immunoturbidimetric method on an automatic biochemical analyzer AU-480 “Beckman Coulter Inc.” (Japan).

Transthoracic echocardiography

Transthoracic echocardiography with pulsed wave, color Dopplerography was performed on a Philips iE33 xMATRIX device (USA) using sensors with a frequency of 3.5 MHz. The size of the heart chambers and indicators of intracardiac hemodynamics were assessed according to the standard methodology adopted by the American Association of Echocardiography.

Standard positions from the parasternal and apical approaches were used along the short and long axes of the LV.

The following indicators were analyzed:

• anterior-posterior size of the LA (cm) in diastole;
• LA end-systolic volume indexed by body surface area (LAVI, ml/m^2);
• LV end-diastolic dimension (LV EDD, cm);
• LV end-diastolic volume (LV EDV, ml^3);
• LV end-diastolic volume indexed to body surface area (LV EDVI, ml^3/m^2);
• LV end-systolic dimension (LV ESD, cm);
• LV end-systolic volume (LV ESV, ml^3);
• LV end-systolic volume indexed to body surface area (LV ESVI, ml^3/m^2);
• LVEF according to Simpson rule (%);
• Right ventricular (RV) end-systolic area (RV ESA, cm^2);
• RV end-diastolic area (RV EDA, cm^2);
• changing in RV area fraction (RV FIP, %);
• systolic excursion of the tricuspid valve annulus (TAPSE, mm).

Doppler echocardiography

Assessment of LV diastolic function was carried out on the 1st day, on the 3rd month of the disease in duplex mode (a combination of two-dimensional and Doppler echocardiography) and tissue Doppler mode, in a cross-section of four chambers from the apical approach.

The following indicators were calculated:

• E, cm/s – early diastolic transmitral flow velocity;
• A, cm/s – late (atrial) transmitral flow velocity;
• E/A, units – the ratio of the early diastolic transmitral flow velocity of the late (atrial) transmitral flow velocity;
• DT, ms – deceleration time of peak E velocity, the time interval from the moment the maximum speed of peak E is reached until the moment the downward section of wave E crosses the zero level;
• IVRT, ms – isovolumic relaxation time (interval from the click of the closure of the aortic systolic flow to the beginning of the transmitral diastolic flow);
• IVCT, ms – time of isovolumetric contraction of the LV (interval between the end of the transaortic and the beginning of the transmitral blood flow);
• e', cm/s – diastolic indicator, speed of movement of the fibrous ring of the mitral valve estimated using tissue Doppler imaging;
• E/e', units – the ratio of the maximum speed of early diastolic filling of the LV and the speed of movement of the fibrous ring of the mitral valve.

Global intraventricular asynchrony (GIVA) and interventricular asynchrony (IVA) were determined.

The determination of the GIVA was carried out in the M - modal mode – as the time difference between the maximum contraction of the interventricular septum and the posterior wall of the LV. A delay between them of more than 130 ms is a marker of global asynchrony.

Interventricular asynchrony was calculated in Doppler mode. This is the difference in intervals from Q on the ECG to the beginning of the aortic flow and from Q on the ECG to the beginning of the pulmonary flow. Interventricular asynchrony occurs if this difference is more than 40 ms.

Coronary angiography

Coronary angiography was performed using a Toshiba apparatus. Contrast agent – Visipaque-320.

During visual analysis of coronary angiography, the following coronary arteries and their branches were assessed: left coronary artery, right interventricular artery, circumflex artery, right coronary artery. The number of affected arteries was assessed. The SYNTAX score was derived from the summation of the individual scores for each separate lesion defined as ≥50% obstruction in vessels ≥1.5 mm. The SYNTAX score was calculated using dedicated software for all patients who underwent coronary angiography (available at https://syntaxscore.org/calculator/syntaxscore/frameset.htm).

Treatment

All patients received antiplatelet agents (aspirin 250 mg with the first dose at the prehospital stage, then 100-125 mg orally, clopidrogrel 300 mg first dose, then 75 mg/day), anticoagulants (unfractionated heparin bolus at a dose of 60 IU/kg followed by infusion of 12-15 IU/kg/h), nitroglycerin (IV 10-50 mcg/min for 24 hours with controlling of heart rate and blood pressure), angiotensin-converting enzyme inhibitors (enalapril 10-20 mg/day), beta blockers (bisoprolol 1.25 mg/day) and statins (atorvastatin 80 mg/day).

Follow-up and Outcomes

All patients were monitored for three months. The follow-up assessment included collecting complaints, physical examination, standard measurement of blood pressure, determination of serum creatinine level with subsequent calculation of GFR using the CKD EPI formula, albumin and protein levels in 24-hour urine, a 12-lead ECG, and transthoracic echocardiography. After three months of observation, the following outcomes were evaluated: rehospitalization, recurrent ACS, progression of HF, and development of CKD.

Statistical analysis

SPSS software (IBM Inc., USA, version 23) was used for statistical analyses of data. Quantitative variables are presented as mean and quartiles (M (Q1-Q3)). To assess the significance of variables, a 95% confidence interval (CI) was calculated. The Kolmogorov-Smirnov test was used to determine the normality of distribution. The *t* test was used to assess the difference between two means for normally distributed data. In the absence of normal distribution of variables, nonparametric research methods were used, the results of which are presented as the median (25th and 75th percentiles): the Mann-Whitney test was used to compare two independent samples, and the Wilcoxon test was used for related variables. Qualitative features were compared using the Chi-Square test.

Pearson's correlation coefficient was used to assess the relationship between two variables if the distributions were normal. The Spearman correlation coefficient was used for non-normal distributions. For the calculation of linear regression analysis between dependent variables – kidney function indicators (GFR, daily microalbunuria, daily proteinuria), outcomes (rehospitalization, recurrence of ACS, progression of HF) – and independent variables (laboratory and echocardiographic indicators), a multiple linear regression analysis was performed. For each dependent variable, regression models of its own type were constructed. In cases where a variable was statistically significant it was included in the adjusted regression model. Ultimately, the model with the best predictive properties was selected for each type. The association of predictors with adverse outcomes (recurrent hospitalization, recurrence of ACS, progression of HF) of patients with CKD was determined using multiple logistic regression analysis. Results were considered significant at the $p<0.05$ level.

Results

We determined that grade I of LV DD occurred in 56.9% of cases, while the grade II of LV DD was found in 43.1% of patients. At the same time, renal dysfunction was observed in 49 (84.48%) patients with NSTE-ACS with HFpEF. In patients with LV DD grade I the renal function disorders were detected in 26 (78.8%) (95% CI 71.2%; 88.8%) cases, while in the group with grade LVDD, impairment kidney function was even more common – in 23 (92.0%) (95% CI 80.7%; 105.8%) patients ($p<0.0001$).

When renal function was examined in detail within the groups, results varied significantly and depended on the severity of LV DD (Table 1). In the group of patients with grade II of LV DD, a decrease in GFR as compared to the first group was detected ($p<0.0001$). It was also found that patients from the 2nd group had higher levels of daily microalbuminuria in contrast to patients with LV DD according to the grade I ($p<0.0001$). In addition, significant differences were observed in the levels of daily proteinuria ($p<0.0001$).

NT-proBNP levels were higher in 2nd group as compared to group 1 ($p<0.0001$).

Analysis of echocardiographic variables demonstrated significantly increased left heart volumes (LAVI – $p<0.0001$, LVEDVI $p=0.001$, LVESV –$p=0.031$) in patients with grade II LVDD as compared to grade I LVDD. There were differences in parameters of diastolic function – higher E/a and E/e` ratios, reduced DT and IVRT in patients of group 2 as compared to group 1 patients (all $p<0.0001$). RV EDA, RV ESA and RV AF were also higher in group 2 as compared to group 1 patients ($p=0.001$, $p=0.002$ and $p=0.03$, respectively).

The results of coronary angiography showed differences in the groups of patients with NSTE-ACS with HFpEF. In the 1st group, 23 patients underwent coronary angiography, while in the 2nd group, coronary angiography was performed on 15 patients. That in the presence of LV DD according to the grade II the number of atherosclerotically affected coronary arteries increases. Three-vessel coronary atherosclerosis in group with grade II of LV DD accounted in 6 (40.0%) patients, two-vessel lesions – in 4 (26.7%), while single-vessel lesions – in 5 (33.3%). In the group of patients with LV DD according to the grade I single-vascular coronary atherosclerosis occurred in 11 (47.8%) of cases, involvement of two coronary arteries was found in 6 (26.1%) of patients. At the same time severe atherosclerosis in three coronary arteries was detected in 6 (26.1%) patients. Calculation of the SYNTAX score showed that more severe degrees of atherosclerotic lesions of the coronary arteries had tendency to be more common in the group of patients with more severe LV DD. (Table 1).

A correlation analysis of laboratory and echocardiographic parameters revealed that the results of renal function (GFR, daily proteinuria and microalbuminuria) were significantly correlated with all parameters of LV diastolic function (Table 2). There is an interesting relationship between renal function and the level of NTpro-BNP ($p<0.0001$), which is explained by an increase in the value of NT-proBNP with increasing diastolic filling of the LV.

Table 1. Baseline demographic, laboratory and echocardiographic values in patients with NSTE-ACS with HFpEF

Variables	1st group (n=33)	2nd group (n=25)	p
Age, years	64 (62; 67)	66 (62.5; 68)	0.317
Sex F/M, %	54.5/45.4	52/48	0.075
BMI, kg/m^2	29.5 (27.8; 30.5)	29.5 (28.4; 31.25)	0.759
Troponin I, ng/ml	0.01 (0.005; 0.02)	0.01 (0.0; 0.02)	0.157
GFR, ml/min/1,73m^2	63.0 (61.5; 64.0)	54.07 (52.5; 56.0)	<0.0001
DMAU, mg/day	33.1 (28.85; 36.35)	53.54 (45.87; 62.28)	<0.0001
DPU, mg/day	94.3 (90.55; 102.4)	164.2 (150.1; 171.8)	<0.0001
NT-proBNP, pg/ml	268.174 (222.878; 334.613)	479.831 (359.998; 527.751)	<0.0001
LA, cm	3.3 (3.2; 3.4)	3.3 (3.16; 3.44)	0.713
LAVI, ml/m^2	32.4 (30.75; 33.95)	35.0 (34.05; 36.85)	<0.0001
LV EDD, cm	4.60 (4.16; 4.82)	4.6 (4.2; 4.8)	0.889
LV ESD, cm	3.4 (3.2; 3.5)	3.4 (3.3; 3.5)	0.892
LV EDV, ml^3	135.4 (128.5; 141.0)	140.29 (137.5; 145.6)	<0.0001
LV EDVI, ml^3/m^2	72.0 (68.4; 76.1)	83.7 (79.4; 85.95)	0.001
LV ESV, ml^3	65.8 (64.15; 67.9)	72.22 (70.91; 75.28)	0.505
LV ESVI, ml^3/m^2	35.0 (34.0; 36.65)	39.37 (38.82; 40.28)	0.031
E, cm/s	46.0 (45.0; 47.0)	58.0 (55.0; 62.0)	<0.0001
A, cm/s	69.0 (65.5; 75.0)	47.0 (38.5; 51.5)	<0.0001
LV E/A, u	0.7 (0.6; 0.7)	1.3 (1.2; 1.5)	<0.0001
e', cm/s	7.1 (6.2; 8.0)	3.9 (3.85; 4.2)	<0.0001
E/e', u	6.5 (5.8; 7.25)	14.7 (14.2; 15.0)	<0.0001
LV DT, ms	218.6 (214.5; 220.85)	174.0 (170.35; 180.05)	<0.0001
IVRT, ms	109.7 (107.55; 113.35)	57.0 (55.05; 58.0)	<0.0001
IVCT, ms	38.0 (36.0; 40.5)	37.0 (35.0; 39.0)	0.272
LV EF, %	52.0 (51.0; 53.0)	52.0 (51.3; 53.2)	0.563
RV EDA, cm^2	29.0 (28.0; 29.5)	30.0 (28.5; 31.0)	0.001
RV ESA, cm^2	16.0 (15.0; 17.0)	17.0 (16.0; 18.0)	0.02
RV AF, %	35.0 (33.0; 36.4)	36.8 (35.0; 38.5)	0.003
TAPSE, mm	17.1 (16.2; 18.4)	18.0 (16.5; 18.0)	0.366
IVA, ms	34.0 (33,0; 35,35)	33.5 (31,75; 34,0)	0.054
GIVA, ms	82.33 (79.5; 85.0)	83.5 (81.95; 85.0)	0.3
SYNTAX score	19.45 (17.65; 28.40)	26.3 (19.7; 31.6)	0.112

A - late (atrial) transmitral flow velocity, BMI - body mass index, DT - deceleration time, DMAU - daily microalbuminuria, DPU - daily proteinuria, E - early diastolic transmitral flow velocity, E/A - the ratio of the early diastolic transmitral flow velocity to the late (atrial) transmitral flow velocity, E/e' - the ratio of the early diastolic filling of the left ventricle and the speed of movement of the fibrous ring of the mitral valve, e' - speed of movement of the fibrous ring of the mitral valve, GFR - glomerular filtration rate, GIVA - global intraventricular asynchrony, HFpEF - heart failure with preserved ejection fraction, IVA - interventricular asynchrony, IVCT - isovolumic contraction time, IVRT - isovolumic relaxation time, LA - left atrium, LAVI - left atrium volume index, LV EDD - left ventricular end-diastolic dimension, LV EDV - left ventricular end-diastolic volume, LV EF - left ventricular ejection fraction, LV ESV - left ventricular end-systolic volume, LV ESD - left ventricular end-systolic dimension, LV EDVI - left ventricular end-diastolic volume index, LV ESVI - i left ventricular end-systolic volume index, NT-proBNP - N-terminal pro b-type natriuretic peptide, NSTE-ACS - non-ST segment elevation acute coronary syndrome, RV AF - right ventricular area fraction, RV EDA - right ventricular end-diastolic area, RV ESA - right ventricular end-systolic area, TAPSE - systolic excursion of the tricuspid valve annulus

Table 2. Relationship between renal and diastolic functions indicators			
Variables	**GFR**	**DMAU**	**DPU**
NTpro-BNP	r=-0.675 (p<0.0001)	r=0.574 (p<0.0001)	r=0.645 (p<0.0001)
LAVI	r=-0.572 (p<0.0001)	r=0.583 (p<0.0001)	r=0.509 (p<0.0001)
E	r=-0.758 (p<0.0001)	r=0.748 (p<0.0001)	r=0.704 (p<0.0001)
A	r=0.598 (p<0.0001)	r=-0.562 (p<0.0001)	r=-0.544 (p<0.0001)
LV E/A	r=-0.746 (p<0.0001)	r=0.681 (p<0.0001)	r=0.672 (p<0.0001)
E/e'	r=-0.704 (p<0.0001)	r=0.595 (p<0.0001)	r=0.628 (p<0.0001)
LV DT	r=0.558 (p<0.0001)	r=-0.622 (p<0.0001)	r=-0.627 (p<0.0001)
IVRT	r=0.649 (p<0.0001)	r=-0.663 (p<0.0001)	r=-0.626 (p<0.0001)
LV EDV	r=-0.267 (p=0.043)	r=0.220 (p=0.096)	r=0.234 (p=0,078)
RV EDA	r=-0.357 (p=0.006)	r=0.405 (p=0.002)	r=0.325 (p=0.013)
RV ESA	r=-0.326 (p=0.013)	r=0.389 (p=0.003)	r=0.474 (p<0.0001)
RV AF	r=-0.278 (p=0.035)	r=0.401 (p=0.002)	r=0.399 (p=0.002)
GIVA	r=-0.369 (p=0,004)	r=0.278 (p=0.035)	r=0.309 (p=0.018)

A - late (atrial) transmitral flow velocity, DT - deceleration time, DMAU - daily microalbuminuria, DPU - daily proteinuria, E - early diastolic transmitral flow velocity, E/A - the ratio of the early diastolic transmitral flow velocity to the late (atrial) transmitral flow velocity, E/e' - the ratio of the early diastolic filling of the left ventricle and the speed of movement of the fibrous ring of the mitral valve, GFR - glomerular filtration rate, GIVA - global intraventricular asynchrony, IVRT - isovolumic relaxation time, LAVI - left atrial volume index, LV EDV - left ventricular end-diastolic volume, NT-proBNP - N-terminal pro B-type natriuretic peptide, RV AF - right ventricular area fraction, RV EDA - right ventricular end-diastolic area, RV ESA - right ventricular end-systolic area

Association of LVDD, NT-proBNP and renal function

Multiple linear regression analysis (Table 3) demonstrated a negative relationship between GFR and NT-proBNP, E/e` and LA size: higher E/e` ratio, larger LA size and higher NT-proBNP levels were associated with lower GFR

values (all p=0.0001). Shorter IVRT was associated with higher DMAU and DPU, while larger RV ESA was related to increased DPU (all p=0.0001). Thus it has been determined that there was a negative relationship of a decrease in the level of renal function is echocardiographic indicators involved in the formation of LV diastolic function, size of the left atrium, NT-proBNP and an increase in the end-systolic area of the RV.

Table 3. Linear regression analysis of indicators affecting GFR, DMAU and DPU						
	Dependent Variables					
Independent variables	GFR R^2=75,8%		DMAU R^2=56,8%		DPU R^2=58,5%	
	B	p	*B*	p	*B*	p
E/e'	-0.716	0.0001				
NT-proBNP	-0.011	0.0001				
LA	-4.534	0.0001				
IVRT			-0.337	0.0001	-0.854	0.0001
RV ESA					4.249	0.047

DMAU - daily microalbuminuria, DPU - daily proteinuria, E/e' - the ratio of the early diastolic filling of the left ventricle and the speed of movement of the fibrous ring of the mitral valve, GFR - glomerular filtration rate, IVRT - isovolumic relaxation time, LA - left atrium, NT-proBNP - N-terminal pro b-type natriuretic peptide, RV ESA - right ventricular end-systolic area

Changes in LVDD and renal function during follow-up

A comparative analysis of groups of patients with NSTE-ACS with HFpEF in the third month showed an improvement in diastolic function in the group of patients with LV DD grade I, but in the 2nd group of patients LV DD remained in grade II.

During prospective observation of patients with NSTE-ACS with HFpEF in the third month, CKD developed in 26 (44.83%) patients. In the 1st group of patients, CKD was found in 3 (9.1%) (95% CI 3.1%; 23.1%) patients, while in the 2nd group, CKD was found in 23 (92%) (95% CI 80.7%; 105.8%) patients (p<0.0001). The decrease in the incidence of CKD in the group of patients with grade I LV DD can be explained by the normalization of diastolic function. While in group of patients with LVDD grade II, no changes in renal function were observed – GFR 54.07 (52.5; 56.0) ml/min/1.73m^2, versus 55.0 (53.2; 56.9) ml/min/1,73m^2 (p=0.36). However, with improvement in LV diastolic function, a positive change in renal function was observed. Thus, GFR of patients in the 1st group of patients after three months was 71.0 (69.0; 73.5) ml/min/1.73m^2 vs. 63.0 (61.5; 64.0) ml/min/1.73m^2 in the first day of hospitalization (p<0.0001). There were positive dynamics after three months in the results of DMAU in the 1st group of patients with improvement in LVDD – 12.1 (9.8; 15.15) mg/day vs. 33.1 (28.85; 36.35) mg/day (p<0.0001). In addition, after three months in the 1st group of patients, with improvement in LVDD, a decrease in DPU was also revealed to 51.8 (43.6; 55.9) mg versus initially 94.3 (90.5; 102. 4) mg (p<0.0001).

Predictors of unfavorable outcomes in NSTE-ACS patients with HFpEF

A prospective three-month follow-up of NSTE-ACS patients with HFpEF shows the development of CKD, the rate of re-hospitalization was 11.4% (95% CI 0.8%; 22.0%, p=0.021), while heart failure symptoms increased in 14.3% (95% CI 3.3%; 26.5%, p=0.008).

Further logistic regression analysis showed that CKD is a significant indicator of the development of an unfavorable prognosis in patients with NSTE-ACS with HFpEF (Table 4). Patients with CKD were 2.474 times more likely to be rehospitalized, 2.120 and 2.647 times more likely to experience recurrence of ACS symptoms and progression of HF as compared to patients without CKD (p<0001, p=0.024 and p<0.0001, respectively).

Table 4. Incidence of adverse outcomes in patients with NSTE-ACS with HFpEF in the presence of CKD

Variables	Odds ratio	95% CI	p
Rehospitalization	2.474	1.748-3.500	<0.0001
Recurrence of acute coronary syndrome	2.120	1.594-2.819	0.024
Progression of heart failure	2.647	1.819-3.851	<0.0001

CKD – chronic kidney disease, HFpEF - heart failure with preserved ejection fraction, NSTE-ACS - non-ST segment elevation acute coronary syndrome

We calculated multiple linear regression analysis to identify the main determinants of unfavorable prognosis in patients with NSTE-ACS with HFpEF, (Table 5). Our study found that prognostically significant indicators for re-hospitalization and the recurrence of ACS were GFR, while possible progression of HF was predicted by the level of daily microalbuminuria.

Table 5. Linear regression analysis of laboratory and echocardiographic parameters influencing unfavorable outcome

	Dependent Variables					
	Rehospitalization R^2=70,8%		Recurrence of ACS R^2=40,0%		Progression of HF R^2=73,2%	
Independent variables	*B*	p	*B*	p	*B*	p
GFR	0.049	<0.0001	0.024	0.007		
LA	-0.507	0.025				
LV EDD	0.223	0.041				
DMAU					-0.020	<0.0001

ACS - acute coronary syndrome, DMAU - daily microalbunuria, GFR - glomerular filtration rate, HF - heart failure, LA - left atrium, LV EDD - left ventricular end-diastolic dimesion

Discussion

Our study found that renal dysfunction in patients with NSTE-ACS and HFpEF correlates with the severity of LVDD. This is supported by the fact that LVDD affects venous return pressure and the subsequent burden on the kidneys, which can exacerbate their function. Indicators of renal function, such as GFR, microalbuminuria, and proteinuria, were significantly associated with LVDD indicators. This suggests that changes in diastolic function can directly impact renal function, possibly through alterations in central hemodynamics and inter-organ interactions. Normalization of LVDD leads to an improvement in renal function. This is explained by the fact that reducing pressure in the pulmonary and systemic circulation helps to improve renal blood flow and reduce renal load. However, prolonged persistence of LVDD is associated with the development of CKD. This may be related to sustained hypertension and renal overload, ultimately leading to functional deterioration of the kidneys.

HFpEF is characterized by impaired LV relaxation during diastole and accounts for more than 50% of all patients with HF (6). Isolated LVDD with preserved LVEF is often observed during echocardiographic evaluation of patients with classic symptoms of HF and these patients may be classified as having diastolic HF. LVDD can be understood as impaired relaxation and/or increased stiffness of the LV myocardium leading to impaired filling during diastole. A stiff incompatible LV with impaired relaxation can lead to increased LV end-diastolic pressure with subsequent increased pulmonary venous pressure. It is unclear why such disturbances in LV diastolic properties cause little or no symptoms in one person but overt HF in another.

Renal dysfunction is one of the most common comorbidities of HFpEF with a prevalence of 30–60%, which increases with the presence of comorbid diseases and with age (7). The high prevalence of renal dysfunction in our study is explained by the presence of ACS. Despite the high incidence of renal dysfunction in HFpEF there are few data on the relationship between renal dysfunction and cardiac structure/function in this population.

Our study as well as the results of previous studies showed that deterioration of renal function is associated with an increase in cardiovascular events and hospitalizations. In a study by Jain et al. (8), CKD was associated with a 1.9-fold increase in all-cause hospitalization. At the same time, the risk of progression of HF in the presence of renal dysfunction increases by 2.2 times compared with normal renal function.

Our study found (Table 5) that prognostically significant indicators for readmission and the development of ACS were GFR and the possible progression of HF was predicted by the level of daily microalbuminuria. A previously presented hypothesis implied that albuminuria did not simply reflect local renal disease but was indicative of more general microvascular endothelial dysfunction (6). It is currently unclear whether microalbuminuria simply reflects more generalized microvascular endothelial dysfunction or may act as a contributing factor to the development of HFpEF by causing damage to the coronary vascular endothelium.

Myocardial ischemia caused by coronary artery disease (CAD) causes myocardial dysfunction. In response to acute ischemia LVDD develops before systolic dysfunction becomes apparent. Diastolic function in CAD changes to varying degrees. During acute ischemia, a distinct abnormality occurs (the LV filling pressure increases) (1). The ratio of diastolic pressure to volume is shifted upward due to altered myocardial relaxation, increased muscle stiffness and ventricular interaction. Acute increase in LA pressure may slightly increase the filling rate given the reduced LV compliance. Myocardial fibrosis due to long-standing atherosclerosis can increase filling pressures but the degree of increase is closely related to intravascular volume status. Shifts in the diastolic pressure-volume relationship reflect loss of chamber elasticity due to increased myocardial stiffness. Thus, LVDD is a more sensitive determinant of CAD than systolic dysfunction.

Asynchronous diastolic filling in ischemic areas of the myocardium can cause global filling failure. Elshafey et al. determined the relationship between the severity of CAD and LV DD (9). It is possible that rapid filling and distension of the coronary bed is an important mechanical driving force for increasing and maintaining LV relaxation. Although total blood flow in a stenotic coronary artery may supply sufficient blood, the rate and extent of early diastolic blood flow may be impaired resulting in prolonged relaxation and changes in the timing and rate of rapid diastolic filling.

Study limitations

Our study had a small number of patients, but this number was sufficient to reveal the significance of the differences. Further recruitment for this study is currently ongoing. Due to the fact that in Kyrgyzstan, coronary angiography is paid for by patients themselves due to financial limitations, not all patients underwent coronary angiography.

Conclusions

1. In NSTE ACS patients with HFpEF, the degree of renal dysfunction was dependent on the severity of left ventricular diastolic dysfunction.
2. Indicators of reduced renal function (decreased GFR, increased DPU and DMAU) in NSTE ACS patients with HFpEF are significantly associated with left ventricle diastolic dysfunction parameters: restrictive pattern E/e` ratio, shorter IVRT and larger right ventricular end-systolic area..
3. When left ventricular diastolic dysfunction is normalized renal function improves in NSTE ACS patients with HFpEF, but at the same time, when left ventricular diastolic dysfunction is maintained for 3 months, chronic kidney disease is formed.
4. We found that in NSTE ACS patients with HFpEF, presence of CKD predicts re-hospitalization, recurrence of acute coronary syndrome and progression of chronic heart failure rates. Glomerular filtration rate, daily microalbuminuria, left atrial and left ventricular end-diastolic size are associated with adverse outcomes.
5. A more pronounced degree of atherosclerotic lesions in patients NSTE ACS with HFpEF has tendency to occur in more severe left ventricular diastolic dysfunction.

Ethics: Informed consent was taken before procedure from patients. This study complies with the Declaration of Helsinki and was performed according to the National Centre of Cardiology and Internal Medicine Ethics Committee approval.
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